comprises: (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, wherein said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3, and a sequence of nucleotides encoding adenovirus fiber protein; and

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2) producing an adenovirus particle.

99. (Amended) The method of claim 98 wherein said exogenous protein is selected from a group consisting of a tumor-suppressor protein, a biologically active fragment thereof that has tumor-suppressor activity, a suicide protein and a biologically active fragment thereof that has activity as a suicide protein.

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REMARKS

A check for the fee for a five month extension of time accompanies this amendment. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1, 2, 4-23, 41, 47, 69 and 94-103 are presently pending in this application. Claims 24-40, 42-46, 48-68 and 71-94, which are drawn to non-elected subject matter, are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional applications to the non-elected subject matter. Claim 3 is also cancelled herein without prejudice or disclaimer.

Claims 1, 2, 4-6, 9, 10, 12, 21-23, 47, 96, 97 and 99 are amended herein to more particularly point out the subject matter by correcting minor and obvious grammatical and antecedent basis errors and to rewrite allowable claims or previously allowed claims as independent claims to incorporate limitations of the independent claim prior to further amendment of the independent claim. The amendment of claim 1 also finds basis at page 34, lines 13 and 23-25. Added claims 100-103 find basis in original claims 6, 7 and 9 and in Example 3. Hence, no new matter is added.

Pursuant to 35 U.S.C. §121 a marked up copy of the amended claims is attached hereto.

DUTY OF DISCLOSURE

A further Information Disclosure Statement is being filed under separate cover. It is noted therein that there are two assignees of the subject matter of this application.

Also, claims in this application were previously rejected under 35 U.S.C. §102(a) as being anticipated by Nemerow *et al.* (International PCT application No. WO 98/13499). In response, it was argued that Nemerow *et al.* is not prior art because this application claims priority thereto. It is noted that such argument is correct only for claims that find basis in Nemerow *et al.* It also is noted that the inventors of Nemerow *et al.* and this application overlap, but are not identical.

CLAIM FOR PRIORITY

In reviewing the file history of the above-captioned application, it appears that any issues regarding amendment of the claim for priority to the converted provisional have been resolved (the note on the continuation page on the Advisory Action indicates that the issue is "desolved", which the undersigned believes is a typographical error, and that the intended word was "resolved.")

As amended, the claim for prioity goes back to the original parent application, U.S. application Serial No. 08/719,806, filed September 25, 1996. The original Declaration reflects such claim, and this application was filed on January 14, 2000, which is before November 29, 2000, and hence the amendment is timely (see, 37 C.F.R. §1.78(B)(5)(ii)(A). A request for a corrected filing receipt will be filed.

It is noted that a Petition, dated January 11, 2000, regarding conversion of the original provisional into a utility application was filed in a parent application and was granted. It appears that it was submitted as Appendix A in a previous response in this case, and was considered as part of the response. The Advisory Action appears to indicate that the claim for priority to the

converted utility application (the subject the Petition (or Appendix A)) was considered and accepted.

OBJECTION TO CLAIMS

Claims 2-10, 12-21 and 69 are objected to as being based on a rejected based claim but would be allowable if rewritten as an independent claim or as based upon an allowable claim. It is respectfully submitted that the amendments of claim 1 should place claims 1 and 11 into condition for allowance, thereby obviating this objection.

THE REJECTION OF CLAIMS 22, 23, 47 and 99 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 22, 23, 47 and 99 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Various bases for this rejection are set forth and each is discussed in turn below. Reconsideration of the grounds for rejection is respectfully requested in view of the amendments of the claims and the following remarks.

Relevant Law

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art, and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Claims need only "reasonably apprise those skilled in the art" of their scope and be "as precise as the subject permits." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. den., 480 U.S. 947 (1987). The Court in Orthokinetics, Inc v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986) held that a claim limitation requiring that a pediatric wheelchair part be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats" is definite. The Court stated:

> The phrase 'so dimensioned' is as accurate as the subject matter permits, automobiles being of various sizes. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, § 112, 2d ¶ requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces in hundreds of different automobiles be listed in the patent, let alone that they be listed in the claims.

1 USPQ2d at 1088.

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. Shatterproof Glass Corp.v. Libby-Owens Ford Col, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular invention and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. §112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (Bendix Corp. v United States, 600 F.2d 1364, 1369, 220 Ct. Cl. 507,514, 204 USPQ 617, 621 (1979); See, also, Carl Zeiss Stiftung v. Renishaw plc, 20 USPQ2d 1094, 1101).

Analysis

1) Claims 22 and 47 are amended as suggested by the Examiner, thereby rendering the rejections of these claims as well as claim 23 on this basis moot.

2) Claim 23 also is rejected as indefinite in the recitation of "said gene under control of an inducible promoter", because it is unclear whether the early

gene and fiber gene are under control of an inducible promoter. As amended claim 23 recites "a gene under the control of an inducible promoter," thereby obviating the grounds for the rejection. It is clear that the complementing gene is under control of an inducible promoter.

3) Claim 99 is rejected as indefinite in the recitation of a "biologiaclly active fragment" of a tumor-suppressive protein and/or a suicide protein because it is unclear what the metes and bounds of such fragments are. As amended herein. the claims recite that the fragments have activity as a tumor suppressor or suicide protein. Such proteins are well known; the Examiner has provided no evidence to suggest that one of skill in the art could not assess whether a particular fragment of a suicide protein or tumor suppressor had the requisite activity. Since these are well known proteins with defined activity, those of skill in the art can readily assess whether a particular fragment of a protein has tumor suppressor activity or suicide protein activity. As amended the claims recite that the fragment has tumor suppressor activity or suicide protein activity, which is not dependent upon structure/function. Rather one of skill in the art can test such a fragment in the same manner that a full length tumor suppressor or suicide protein is tested. Therefore, the metes and bounds of the claim are not unclear, but are a definite as the subject matter permits.

THE REJECTION OF CLAIMS 1 AND 11 UNDER 35 U.S.C. § 102

1) Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Logan *et al.* or Sheay *et al.*, which discloses nucleic acid molecules that comprise a partial exon 1 and exons 2 and 3 from Ad2 or Ad5. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.)

1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

The claims

Claim 1 is directed to an isolated nucleic acid molecule that comprises a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons or (b) first, second and third TPL exons such that at least two are different TPL exons, wherein said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3. Claim 11 is directed to a plasmid that contains the nucleic acid molecule of claim 1.

Differences between the disclosure of *et al.* and the claimed subject matter

Logan *et al.* discloses nucleic acid molecules that include a partial exon 1 and exons 2 and 3 from Ad5, and Sheay *et al.* discloses nucleic acid molecules that include an Ad2 tripartite leader. Claim 1 requires that at least two of the exons are different (*i.e.* the two sequences are "not normally found together in nature", see page 34, lines 23-25). Therefore, claim 1 differs from Logan *et al.* since it requires a complete exon 1, and differs from Sheay *et al.* and from isolated viral nucleic acid because it requires that at least two of the exons are different. Therefore, neither Logan *et al.* nor Sheay *et al.* anticipate claim 1 or claim 11, which is dependent on claim 1.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Von Seggern *et al.*

Serial No.: 09/482,682
Conf. No.: 7337

Filed: January 14, 2000

For: *ADENOVIRUS VECTORS, PACKAGING CELL LINES, COMPOSITIONS, AND METHODS FOR PREPARATION AND USE*

Art Unit: 1648

Examiner: Foley, S.A.

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Jonathan Ong

MARKED UP SPECIFICATION AND CLAIMS (37 C.F.R. § 1.121)

Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

IN THE SPECIFICATION:

At page 1, amend lines 4-7, as follows:

This application is a continuation-in-part of U.S. Application Serial No. 09/423,783, which entered the U.S. National Stage on [filed] November 12, 1999, is the U.S. National Stage of International PCT application No. PCT/EP97/05251, filed September 24, 1997, and claims the benefit of the filing date of U.S. Application Serial No. 08/719,806, filed September 25, 1996. [and claims the benefit of the filing date of U.S. Provisional Application 60/115,920 filed January 14, 1999.] This application also is a continuation-in-part of U.S. Application Serial No. 09/795,292, filed January 14, 1999 (converted to a U.S. Non-Provisional Application from U.S. Provisional Application No. 60/115,920, filed January 14, 1999), also is a continuation-in-part of International application No. PCT/EP97/05251, filed September 24, 1997, and also is a continuation-in-part of U.S. Application Serial No. 08/719,806, filed September 25, 1996.

The contents of U.S. application Serial No. 09/423,783 [each application] and U.S. Application Serial No. 09/785,292 (converted from U.S. Provisional Application No. 60/115,920), are incorporated herein by reference.

IN THE CLAIMS:

Please amend claims 1, 2 4-6, 9, 10, 12, 21-23, 47 and 96, 97 and 99 as follows:

1. (Amended) An isolated nucleic acid molecule comprising:

a sequence of nucleotides encoding an adenovirus tripartite leader (TPL)[nucleotide], wherein the [said] TPL-encoding sequence of nucleotides [nucleotide sequence comprising] comprises: (a) first and second different TPL exons or (b) first, second and third [same or different] TPL exons such that at least two are different TPL exons, wherein said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3.

2. (Amended) [The] An isolated nucleic acid molecule, [of claim 1] comprising: a sequence of nucleotides encoding an adenovirus tripartite leader (TPL) that comprises (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon, wherein the sequence of nucleotides encoding a TPL is operatively linked to an intron containing an RNA processing signal.

4. (Twice Amended) The isolated nucleic acid molecule of claim 2, wherein said intron is native adenovirus intron 1.

5. (Amended) [The] An isolated nucleic acid molecule,[of claim 1] comprising a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein said TPL nucleotide sequence is [shown] set forth in SEQ ID NO: 32.

6. (Twice Amended) [The] An isolated nucleic acid molecule,[of claim 1] comprising an adenovirus tripartite leader (TPL) nucleotide sequence, said

TPL nucleotide sequence comprising (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial exon 1, complete TPL exon 2 and complete TPL exon 3 and further comprising a promoter and a sequence of nucleotides that [nucleic acid sequence which] encodes an adenoviral structural protein, operatively linked to said promoter and said TPL-encoding sequence of nucleotides.

9. (Amended) The isolated nucleic acid molecule of claim 7, wherein said molecule is contained in a plasmid selected from the group consisting of plasmids [pCLF,] pDV60, pDV67, pDV69, pDV80 and pDV90.

10. (Amended) The isolated nucleic acid molecule of claim 9, wherein said molecule has a nucleotide sequence selected from the group consisting of sequences shown in [SEQ ID NO: 8,] SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 47, SEQ ID NO: 64 and SEQ ID NO: 65.

12. (Amended) An adenovirus vector packaging cell line, comprising:

i) a stably integrated nucleic acid molecule [or claim 1], comprising an adenovirus tripartite leader (TPL) nucleotide sequence, said TPL nucleic sequence comprising (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon; and

ii) an operatively-linked promoter and a nucleic acid sequence [which] that encodes an adenovirus structural protein,

wherein [said] the sequence of nucleotides that encodes the TPL [sequence] consists essentially of a first TPL exon operatively linked to a complete second TPL exon operatively linked to a complete third TPL exon.

21. (Amended) The cell line of claim [20] 12, wherein said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome.

22. (Once Amended) The cell line of claim 21, wherein said cell line [further produces an adenovirus protein and thereby complements a deficient adenovirus gene in said vector genome, and wherein said cell line complements] expresses an adenovirus early protein gene and a fiber gene.

23. (Amended) The cell line of claim [22] 21, wherein [the] deletion of [said] a deficient [adenovirus] viral gene is complemented by the expression of [said] a gene under the control of an inducible promoter.

47. (Amended) The method of claim [46] 41, wherein:

said nucleic acid molecule is a nucleic acid molecule comprising an adenovirus tripartite leader (TPL) nucleotide sequence, said TPL nucleotide sequence comprising (a) first and second different TPL exons or (b) first, second and third different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3; and

said molecule further comprises a sequence encoding adenovirus fiber protein.

96. (Amended) A method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises:

a) a stably integrated nucleic acid molecule [of claim 1], comprising:

a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, wherein said TPL

exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3; and

b) said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome[,]; and

2) producing said adenovirus particle.

97. (Amended) A method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises: the stably integrated nucleic acid molecule, [of claim 1] comprising:

a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, wherein said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3, and a sequence of nucleotides encoding adenovirus fiber protein[,]; and

2) producing an adenovirus particle.

99. (Amended) The method of claim 98 wherein said exogenous protein is selected from a group consisting of a tumor-suppressor protein, a biologically active fragment thereof that has tumor-suppressor activity, a suicide protein and a biologically active fragment thereof that has activity as a suicide protein.